Missed opportunities: unnecessary medicine use in patients with lung cancer at the end of life: an international cohort study

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Aims

To (1) examine the prescribing of preventative medication in a cohort of people with advanced lung cancer on hospital admission and discharge across different healthcare systems; (2) explore the factors that influence preventative medication prescribing at hospital discharge.

Methods

A retrospective cohort study across two centers in the United Kingdom and the United States. The prescribing of preventative medication was examined at hospital admission and discharge for patients who died of lung cancer; a zero-inflated negative binomial regression model was used to exam the association between preventative medications at discharge and patient- and hospital-based factors. Classes of preventative medication included: vitamins and minerals, anti-diabetic, anti-hypertensive, anti-lipid, and anti-platelet medications.

Results

In the UK site (n=125 people), the mean number of preventative medications was 1.9 (SD ± 1.7) on admission, and 1.7 (SD ± 1.7) on discharge, whilst in the US site (n=191 people) the mean was 2.6 (SD ± 2.2) on admission and 1.9 (SD ± 2.2) on discharge. The model found a significant association between the number of preventative drugs on admission and the number of preventative medications on discharge; the model also found a significant association between the total number of drugs on discharge and the number of preventative medications on discharge. Other indicators related to patient and hospital factors were not significantly associated with preventative medications supplied on discharge.

Conclusions

The use of preventative medication was common in lung cancer patients, despite undergoing discharge. Patient-based and hospital-based factors did not influence the prescribing of preventative medication

What is known about this subject?

- The presence of multi-morbid conditions is highly common in a lung cancer population.
- It is common for this patient group to have complex, costly and often inappropriate medication regimens.
- This patient group is frequently hospitalized in the last year of life.

What this study adds?

- The use of preventative medication is common in lung cancer patients is common, which is evident across different healthcare systems
- There is no association between preventative medication at discharge and patient-based (e.g stage of cancer), and hospital-based factors (e.g time spent in hospital).
- Deprescribing interventions directed towards reducing preventative medication use could be implemented at the point of hospital discharge.

Background

Lung cancer is the most common cancer in the world with around 1.8 million new cases diagnosed annually.[1] It is the most frequent cause of cancer-related mortality, accounting for approximately 1.5 million deaths each year – roughly equating to around 1 in 5 of all cancer-related deaths.[2] Lung cancer, like the majority of other cancers, is predominately a disease of older people: around two in three cases are reported in people aged over 65 years, while the mean age of diagnosis is 70 years.[3]

Due to age as well as common risk factors, the presence of multi-morbid conditions – including cardiovascular disease, cerebrovascular disease, and chronic obstructive pulmonary disease (COPD) – is highly common in a lung cancer population.[4] The presence of these chronic conditions is accompanied by the chronic use of medications to maintain disease control or to treat symptoms associated with these conditions or to prevent further worsening of them. The overall effect of this paradigm is that polypharmacy is common and the pill burden is high amongst this patient group.[5-6] This is challenging, particularly for medication used in the context of primary or secondary prevention: a recent systematic review showed that many preventative medications are inappropriately prescribed in the context of life limiting illnesses, such as lung cancer; the review identified vitamins and minerals, anti-diabetic, anti-hypertensive, anti-lipid, and anti-platelet medications, as preventative medication with questionable benefit.[7] In addition, previous research has also demonstrated that inappropriate medication use in a palliative setting could increase the risk of the patient developing severe drug-drug interactions, possibly resulting in hospitalization or even death.[8]

Previous work has shown that lung cancer patients are frequently hospitalized in their last year of life – perhaps more so than patients with any other type of cancer.[9] For example, Mayer and colleagues showed that out of 37,760 cancer-related Emergency Room (ER) visits, 26.9% were attributable to lung cancer patients (compared to 6.3%, 6.0%, and 7.7% of visits

for breast, prostate, and colorectal patients respectively).[10] Common reasons for the hospitalization of lung cancer patients included pain, respiratory distress, and GI issues.[10] Given this observation, and the fact that lung cancer patients often have complex, costly, and burdensome medication regimens, it is not clear how episodes of hospitalization – or prolonged periods of time spent in hospital – influence or change a patient's medication, or indeed, how this varies according to healthcare system. In the UK, for example, patients with advanced disease receiving cancer therapy may be cared for in hospice care for a significant time before death and may still be admitted to the hospital.[11] In the US, patients are referred to hospice care late in the disease process, with a median length of stay in hospice of 19 days for patients with cancer.[12] We hypothesized that a hospital stay would present an opportunity to reduce medications with questionable benefit, and thus, through medicine optimization and hospital discharge, it would be more likely that preventative medication would be discontinued.

This work, therefore, aimed to (1) examine the prescribing of preventative medication in a cohort of people with advanced lung cancer on hospital admission and discharge across different healthcare systems; and, (2) explore the factors that influence preventative medication prescribing at hospital discharge.

(1) describe preventative medication prescribing in a cohort of lung cancer patients pre- and post- hospital admission across different healthcare systems; and (2) to explore the factors that influence preventative medication prescribing at hospital discharge in a cohort of lung cancer patients.

Methods

Setting

To meet our study aims, two tertiary care centers were chosen as sites of data collection: MD Anderson Cancer Centre, Houston, Texas, US; and, The Newcastle Hospitals Foundation Trust, Newcastle-upon-Tyne, UK. MD Anderson solely focuses on cancer care, and has around 1.5 million patient contacts per year, with patients who have Medicare, private insurance, or other means of healthcare coverage, whilst The Newcastle Hospitals provides all aspects of healthcare, including cancer care, and has around 1.7 million patient contacts per year, the vast majority of which are managed through the National Health Service (NHS). There are approximately 1800 inpatient hospital beds across The Newcastle Hospital Foundation Trust and, for MD Anderson, there are around 600 inpatient beds.[13-14] Study approval and registration was obtained from each site: as this was a retrospective study on deceased patients, this work was considered 'not human subject research' as defined by the Federal Regulations. In view of this, full IRB approval was not required, and The Waivers of Informed Consent and Authorization were granted.

Design

This was a retrospective cohort study of medication use at hospital admission and hospital discharge during the hospitalization prior to death for patients who died of lung cancer.

Inclusion criteria

Patients were included in the analysis if they had primary non-small cell lung cancer or small cell lung cancer, were admitted to a hospital study site at least once within the last 6 months of life, and died in 2013. A hospital admission was defined as an encounter in which a patient received continuous care at the hospital as an inpatient.

Exclusion criteria

Any patient who received care exclusively as an outpatient in a study site was excluded from the study. Patients who died in hospital were excluded. Patients were excluded if the hospital admission was unrelated to the lung cancer (e.g. road traffic accident).

Data sources

Data relating to patient deaths, cancer type and staging were obtained from either the electronic medical record (MD Anderson) or from cancer registries linked to the study site (Newcastle). Patient and medication data were then extracted from each hospital computer system and included the following: medications on admission, medications on discharge, length of hospital admission, number of hospital admissions in last 6 months of life, and co-morbidities. Each medication was classified according to British National Formulary (BNF) category; all continuous and 'when required' medications were included in the analysis. Preventative medication with questionable benefit was defined in one of five categories: vitamins and minerals, anti-diabetic, anti-hypertensive, anti-lipid, and anti-platelet medications, based on a previous systematic review.[7] Co-morbidity was calculated according to the Charlson Comorbidity Index, although for our calculations, we removed the scores related to tumour without metastases, and metastatic solid tumour for lung cancer, but included other cancers.[15]

Outcome measures

The primary outcome in this study was the number of preventative medicines prescribed on hospital discharge. We defined preventative medicines as drugs for diabetes, hypertension, hyperlipidemia, antiplatelet agents, and vitamins/minerals. We included clinical

and demographic variables, hospitalization variables, and medication use variables as possible predictors of discharge preventative medicine use.

Statistical analysis

Patient age, gender, cancer diagnosis, cancer stage, Charlson Comorbidity Index, hospital length of stay, length from discharge to death, and the number of preventative medicines used in each category, were stratified by the US and the UK cohorts. Means, medians, standard deviation, and range for each measure were reported. The McNemar test was then used to compare preventative medicine use at admission and at discharge to determine whether there was a significant difference in the proportion of patients taking any preventative medicine or preventative medicines in each of the five categories. In multivariable analysis, we conducted the same analyses for the UK and the US cohorts. With the outcome of number of preventative medicines on discharge, we constructed zero-inflated negative binomial regression models to account for excess zeros in the number of preventative drugs at discharge. The decision to use a zero-inflated negative binomial regression model was made *a priori* based on our understanding of the data. We first built models based on groups of variables, including clinical and demographic variables (age died, gender, cancer type, cancer stage, comorbidity), hospital variables (length of stay, number of hospitalizations in the last 6 months of life), and medication use (total preventative medicine use at admission and preventative medicine use in each of the 5 categories at admission and discharge, as well as total medicine use at admission and discharge). Except for gender, cancer type, cancer stage, comorbidity, receipt of types of preventative medicines (yes/no), the remaining variables were continuous. For the US data only, we included palliative care consultation as a single, ungrouped variable in the models. We built stepwise models by adding these groups of variables and did stepwise deletion by groups of variables and then further by individual variables, retaining variables in the model

with $p<0.1$. The likelihood ratio test was used to compare models at each step (Appendix 1). The final US and UK models had some important differences in significant variables, and we took a final step to investigate whether similar models were appropriate for both sets of data. A $p<0.05$ was considered statistically significant. All analyses were conducted separately for the UK and US cohorts. The UK data were analysed using SAS version 9.1, and the US data were analysed using STATA version 14. No statistical comparisons were made between the two cohorts.

Results

Participant Characteristics

In 2013, a total of 185 lung cancer patients died who received care in the UK study site, whilst 349 died in the US study site. From the UK data, 19 patients died 6 months after their last hospital admission, 37 patients died in hospital, and 4 patients had missing data (cancer stage, information relating to medications on admission, and information relating to medications on discharge). From the US data, 109 patients died in hospital, 29 were treated only in the ER or on observation status without inpatient admission, 14 had cancers other than non-small cell or small cell lung cancer, 3 patients had admissions unrelated to lung cancer, and 3 patients had missing data. In total, there were 125 patients (UK) and 191 patients (US) included in the analysis.

Characteristics

The median patient age was 73 years for the UK site (range 48-98 years), and 65 years for the US site (range 22-90 years); there were more males than females for both study sites, whilst the majority of people presented with stage IV lung cancer; non-small cell cancer lung cancer (NSCLC) was more common than small cell lung cancer (SCLC). Of the UK cohort,

62.4% had a Charlson score of 1 or higher, and 52.4% of the US cohort had a score of 1 or higher (Table 1).

In the last 6 months of life, repeated hospital admissions were common at both study sites: for the UK site, the mean number was 2.0 (SD ± 1.0), whilst for the US site, the mean number was 1.9 (SD ± 1.0). The mean length of each hospital admission was 10.9 days (SD ± 9.0) for the UK site, and 7.8 days for the US site (SD ± 7.4), whilst patients at both sites, on average, lived around 6 weeks after their last hospital admission. Polypharmacy, defined as 5 ≥ medications, was also common at both sites (observed in 81.6% and 93.7% of individuals admitted to hospital at UK and US sites, respectively), with the total number of medications increasing after each hospital admission (Table 2).

Preventative medication

The mean number of preventative medications on admission was 1.9 (SD ± 1.7) and 2.6 (SD ± 2.2) and, for discharge, the mean number was 1.7 (SD ± 1.7) and 1.9 (SD ± 2.2) for UK and US sites, respectively. On admission, approximately 73 per cent of patients received a preventative medication for the UK site, whilst for the US site approximately 80 per cent of patients received a preventative medication. Overall, the number of preventative medications reduced at discharged to 63 per cent for the UK site, and 69 per cent for the US site; this change was significant for UK and US sites (Table 3). The most common prescribed preventative medication were the anti-hypertensive agents at the UK site, and vitamin and minerals at the US site; the least common prescribed medications were the anti-diabetic agents, which was apparent for both sites. All prescribed preventative medication categories reduced after discharge, apart from anti-diabetic agents and vitamins and minerals (UK), which increased, although this was not statistically significant, and anti-hypertensive medication (US), which remained constant.

Modeling variables

Overall, the mean number of preventative medications was less on hospital discharge compared to admission. When we examined how preventative medication at discharge was related to other factors, the zero-inflated negative binomial regression model found a significant positive association between the number of preventative drugs on admission and the number of preventative medications on discharge; for example, in the UK model, for every 1 preventative drug at admission, the number of preventative medications at discharge will increase by 1.27, expressed as Incidence Rate Ratio (IRR) (95% confidence Intervals (CI): 1.17, 1.39); similarly, in the US model, for every 1 preventative drug at admission, the number of preventative medications at discharge will increase by 1.13 IRR (95% CI: 1.06, 1.20). There was also a significant positive association between the total number of drugs on discharge and the number of preventative medications on discharge, which was evident at both UK and US study sites (Table 4). In the US model only, there were significant associations between total drugs on admission with an IRR of 0.95 (95% CI: 0.92, 0.97), having a palliative care consultation with an IRR of 0.73 (95% CI: 0.58, 0.92), and total medication at discharge with an IRR of 1.10 (95% CI: 1.08, 1.13). None of the other indicators (age, cancer stage, cancer type, co-morbidity, length of hospital admission, number of hospitalizations) were significantly associated with preventative medications on discharge, and their addition/removal did not significantly affect our models (Appendix 2).

Discussion

This paper is the first to describe the prescribing of preventative medication in a cohort of lung cancer patients at hospital admission and discharge across different healthcare systems. We have identified a number of key findings that may be of importance to healthcare

practitioners and policy makers: (1) for lung cancer patients who are admitted to hospital, polypharmacy is common; (2) the mean number of medications a hospitalized lung cancer patient is prescribed increases after hospital admission; (3) the prescribing of preventative medications is common amongst hospitalized lung cancer patients; and, (4) patient factors (such as age, cancer stage, cancer type, co-morbidity, and number of days between discharge and death) and hospital factors (such as length of hospital admission, and number of hospitalizations) were not associated with the prescribing of preventative medication.

While this is the first study to specifically assess prescribing of preventative medication in lung cancer patients, other studies have explored prescribing and medicines use for patients who are at end of life. Currow and colleagues, for example, showed that, in a cohort of palliative care patients, as death approaches, the number of medications increases from 4.9 to 6.4 – primarily as a result of people using more symptom specific medications.[16] Of note, the same study also showed the number of potentially inappropriate medications, as assessed using the Beers criteria, also increased as death approaches.[16] Other studies have explored the prescribing of specific classes of medication in the context of limited life expectancy: for example, Pearson and colleagues showed more than 30 per cent of cancer patients were dispensed statins within 30 days of death,[17] whilst Bayless and colleagues revealed, in a cohort of cancer patients, more than 60 per cent of individuals continued with statin therapy for 2 years after their diagnosis.[18] Our findings lend support to the literature, and show that lung cancer patients who are admitted to hospital are commonly discharged with preventative medication; this appears to have been the continuation of current medication, as opposed to initiating new preventative medication.

In terms of developing an intervention to reduce polypharmacy and rationalize medications in lung cancer patients – or possibly other life limiting illnesses – this work is significant. Indeed, our work shows that the point of discharging a patient from hospital might

be an appropriate place to develop an intervention to reduce – or to start the process of reducing – burdensome preventative medication that is no longer appropriate given a patient's reduced life expectancy. Further work should explore the nature of the intervention, but it is encouraging that, at the US site, a consultation with a palliative care clinician did appear to be associated with less preventative medication on discharge. This is consistent with a previous study in the inpatient palliative care unit at the same US setting that found among 100 consecutive patients admitted to the unit, medications increased from a mean of 9.2 to 10.1, with an increase in symptomatic medications and a reduction in medications for comorbid conditions.[19]

Previous literature has also shown that a pharmacist intervention at the point of discharging has reduced the level of inappropriate prescribing in a general older population.[20-21] Given the important role of clinical pharmacists in both UK and US discharge processes, they should play a key role in delivering any intervention aimed at reducing inappropriate medication in this patient population. It is clear, however, that any such intervention to reduce inappropriate or burdensome medication should embrace the principles of deprescribing. Indeed, the term 'deprescribing', recently defined by Reeve and colleagues, as *the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcome*,[22] has received a great deal of recent attention in the literature. The process of deprescribing has recently been reviewed,[23] and the literature suggests that in order to achieve a successful outcome many factors need to be considered, including patient-based (e.g. patient misalignment with goals of care),[24] and those involving the caregiver.[25] Another issue toward deprescribing is the lack of robust evidence demonstrating the effectiveness of deprescribing preventative medication in patients with life limiting illness. Page and colleagues have shown that deprescribing in older adults appears to be safe and feasible,[26] although, to

date, Kutner and colleagues are the only group to publish a randomised clinical trial specifically addressing the issue of deprescribing medication in people with life limiting illness. The trial, which discontinued statin therapy in a cohort of patients with advanced life limiting illness, showed that stopping statin therapy is safe, and is associated with reduced costs and improved quality of life.[27] Given the high prevalence of other preventative medication identified in our cohort of patients, other trials, exploring the cessation of antihypertensive agents, and anti-diabetic agents appear to be warranted. A small scale study has, however, shown many palliative care patients with previously diagnosed hypertension despite having low blood pressure, and, in some cases, symptoms of postural hypotension, are still using antihypertensive medication.[28]

While we believe our results are robust, and have important implications for the way in which medications are prescribed to lung cancer patients, we do acknowledge our work has several limitations: firstly, we did not assess the appropriateness of preventative medication, as we just reported on the prescribing. It is possible that some of the preventative medication was prescribed appropriately (for example, ACE inhibitors in the case of advanced heart failure); secondly, only including lung cancer patients who were admitted to hospital, may not give a true account of the medication histories for all lung cancer patients, given that it is possible that those admitted to hospital had more complex medication regimens. We do not know if patients were discharged with a plan for medication reduction after discharge. We also were not able to collect information on site of discharge or discharge to hospice care, which might be particularly important in the US cohort. We would, therefore, urge that our results are interpreted in view of these limitations. In terms of study strengths, we believe that collecting data across two healthcare systems (the UK, and the US) is a key strength of the study, and this adds international context to our work.

Conclusion

Polypharmacy is common in hospitalised lung cancer patients; the use of preventative medication remained high among such patients, despite undergoing hospital discharge. Patient-based and hospital-based factors did not influence the prescribing of preventative medication. There may be scope to develop an intervention that embraces the principles of deprescribing at the point of hospital discharge to reduce inappropriate prescribing in lung cancer patients.

Conflicts of Interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Table 1: Study participant characteristics for UK and US sites

		UK (%) n=125	US (%) n=191
Gender	Female	48.8	46.6
	Male	51.2	53.4
Cancer type	NSCLC	85.6	86.4
	SCLC	14.4	11.5
	Other	0.0	2.1
Staging	1A	0.8	2.1
	1B	3.2	0.0
	IIA	1.6	0.0
	IIB	1.6	0.5
	IIIA	8.8	6.8
	IIIB	16.0	2.6
	IV	68.0	88.0
Charlson co-morbidity index	0	37.6	47.6
	1	44.8	23.6
	2	9.6	17.3
	3	6.4	6.8
	4	0.8	2.1
	5	0.0	1.6
	6	0.8	0.0
	7	0.0	0.5
	8	0.0	0.5

Table 2: Hospital admission and discharge characteristics for study participants

	UK (n=125)			**US (n=191)**		
Indicator	Mean, SD	Median	Range	Mean, SD	Median	Range
Age (years)	72.8 ± 10.5	73	48-98	63.8 ± 10.9	65	22-90
Length of hospital admission (days)	10.9 ± 9.0	8	1-37	7.8 ± 7.4	6	1-49
Number of hospital admission within 6 months of life	2.0 ± 1.0	2	1-5	1.9 ± 1.4	1	1-10
Number of days discharged before death	43.3 ± 46.0	28	1-178	38.4 ± 40.7	22	1-190
Total preventative drugs on admission	1.9 ± 1.7	2	0-7	2.6 ± 2.2	2	0-10
Total preventative drugs at discharge	1.7 ± 1.7	2	0-7	1.9 ± 2.0	1	0-8
Total drugs on admission	8.8 ± 3.8	9	1-18	11.6 ± 5.0	11	0-26
Total drugs discharge	10.3 ± 4.3	11	1-20	12.1 ± 4.7	12	2-28

Table 3: Number of patients with preventive medication at admission and at discharge.

	UK (n=125)			US (n=191)		
Preventive Medicine Type	N (%) at admission	N (%) at discharge	P-value[a]	N (%) at admission	N (%) at discharge	P-value[a]
Anti-diabetic	8 (6.4)	11 (8.8)	0.375	23 (12.0)	21 (11.0)	0.75
Anti-hypertensives	59 (47.2)	44 (35.2)	0.001	97 (50.8)	97 (50.8)	1.000
Anti-lipid	57 (45.6)	40 (32.0)	<0.001	61 (31.9)	44 (23.0)	0.032
Anti-platelet	38 (30.4)	30 (24.0)	0.057	39 (20.4)	33 (17.3)	0.307
Multivitamins and minerals	30 (24.0)	36 (28.8)	0.286	106 (55.5)	73 (38.2)	<0.001
Any preventive medicine	91 (72.8)	79 (63.2)	0.017	152 (79.6)	132 (69.1)	0.002

[a]difference between number at admission and number at discharge, using the McNemar test

Table 4. Zero inflated negative binomial regression models examining association between of total preventative drug at discharge with related factors.

	United Kingdom (n=125)
Indicator	IRR, 95% CI
Number of days admitted	0.99 (0.97-1.01)
Total drugs at admission	0.95 (0.90-1.01)
Total drugs at discharge	1.08 (1.03-1.14)
Total preventative drugs at admission	1.27 (1.17-1.39)
	United States (n=191)
Indicator	IRR, 95% CI
Palliative care consultation	0.73 (0.58-0.92)
Total drugs at admission	0.95 (0.92-0.97)
Hypertensive drugs at admission	1.33 (1.18-1.50)
Total drugs at discharge	1.10 (1.08-1.13)
Total preventative drugs at admission	1.13 (1.06-1.20)
Anti-platelet drugs at admission	1.25 (1.00-1.54)

Appendix 1. Likelihood ratio test comparing the saturated model and final model to ensure that no substantial loss of information between the saturated model and the final most parsimonious model

Country	Models	-2 Log likelihood (-2LL)	# parameters	df	Difference in -2LL	*P value*
UK	Saturated model	303.580	22	18	8.579	0.968
	Final model	312.159	4			
US	Saturated model	592.561	24	19	-40.441	1.000
	Final model	552.012	5			

Appendix 2a. Type 3 test from zero inflated negative binomial regression models for variables not included in the final model for UK data

	UK data		
Indicators	*DF*	*Chi-square*	*P value*
Gender	1	0.07	0.785
Age	1	0.49	0.486
Cancer type	1	0.01	0.931
Cancer stage	7	2.14	0.952
Comorbidity	1	0.04	0.849
Length of hospital admission	1	3.18	0.075
Number of hospitalizations	1	0.20	0.657

Appendix 2b. Negative binomial regression results for variables not included in the final model for US data

Indicators	*Chi-square*	*P value*
Gender	1.40	0.163
Age	-0.19	0.848
Cancer type		
Small cell lung cancer	1.28	0.202
Other	-0.83	0.406
Cancer stage		
IIB	0.80	0.422
III	1.31	0.189
IIIB	1.17	0.241
IV	0.71	0.480
Comorbidity (CCI)		
1	1.35	0.175
2	0.53	0.596
3	1.55	0.121
4	0.88	0.380
5	1.26	0.207
7	-0.11	0.908
8	0.67	0.505
Length of hospital admission	0.42	0.673
Number of hospitalizations	0.57	0.569
Number of diabetes medications at admission	-1.50	0.133
Number of lipid lowering drugs at admission	-2.07	0.038

Appendix 3. Variance Inflation factor to check for multicollinearity between the variables included in the final model. Value between 1 and 10 are considered acceptable (Kutner MH, Nachtsheim C, Neter J. (2004). Applied linear regression models. McGraw-Hill/Irwin.

Variables	Variance Inflation Factor (VIF)	
	UK data	US data
Length of admission (days)	1.027	-
Number of drugs on admission	2.091	1.86
Total preventative drugs (admission)	1.321	2.41
Number of drugs on discharge	1.766	1.53
Palliative care consultation	-	1.11
Hypertensive drugs (admission)	-	1.63
Antiplatelet drugs (admission)	-	1.29